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Review

Viral hepatitis screening guideline before biological drug use in rheumatic patients

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Abstract

Biological drugs (tumor necrosis factor inhibitors, rituximab, tocilizumab, abatacept, and tofacitinib) are important treatment alternatives in rheumatology, particularly for resistant patients. However, they may cause hepatitis B virus (HBV) and hepatitis C virus (HCV) reactivation; for instance, HBV reactivation may occur in a patient who is an inactive hepatitis B surface antigen (HBsAg) carrier or who has resolved HBV infection. Therefore, the screening of patients before biological treatment and the application of a prophylactic treatment, particularly with respect to latent HBV infections, are recommended when necessary. This guideline covers pre-treatment screening and follow-up recommendations, if required, with respect to viral hepatitides in rheumatology patients who are planned to be given biological drugs. Although this guideline is prepared for biological disease-modifying antirheumatic drugs (DMARDs), it is recommended to be used also for target-oriented DMARDS and medium–high dose corticosteroids (>7.5 mg prednisolone/day equivalent). It should be considered that the reactivation risk is higher when more than one immunosuppressive drug is used.

Keywords: Viral hepatitis, biologic drugs, rheumatic patients

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Introduction

Biological drugs are drugs that specifically target one of the immune or genetic mediators that play a role in the development process of a disease (1). These drugs are important treatment alternatives in rheumatology, particularly for resistant patients (2). Biological drugs [tumor necrosis factor (TNF) inhibitors, rituximab, tocilizumab, abatacept, tofacitinib] effectively suppress disease activity. However, they can cause some side-effects, such as latent tuberculosis (TB) reactivation, hepatitis B virus (HBV) reactivation, and demyelinating diseases because they are target l-directed molecules (3). Therefore, the screening of patients with respect to some diseases before biological treatment and the application of prophylactic treatment, particularly with respect to latent TB or HBV infections, are recommended when necessary.

HBV is transmitted through parenteral, vertical, sexual, and horizontal routes. One-third of the world's population is infected by HBV (4). Currently, it is estimated that 240 million people are HBV carriers worldwide. HBV infection becomes chronic (HBsAg positivity longer than 6 months) at varying rates, according to the age at which HBV infection occurs. The rate of becoming an HBV carrier following vertical contamination is 95%, while the rates of becoming HBV carriers after infections during adolescence or in adult age are much lower, being approximately 15–20% and 4–5%, respectively. Hepatitis C virus (HCV) is an RNA virus transmitted through parenteral, vertical, and sexual routes. It is currently estimated that more than 185 million people in the world are infected with HCV (5, 6). HCV is removed from the body of 30–50% of patients within 6 months after infection, while infection becomes chronic in 50–70% of patients.

According to the results of the HBV and HCV prevalence study in Turkey, the HBV carrier rate was 3.9%, while exposure to HBV was 30.4%, and anti-HCV positivity was 0.9% (7). HBV and HCV incidences in patients with rheumatoid arthritis and ankylosing spondylitis were found to be similar to those in the prevalence study (8).

In rheumatic diseases, HBV and HCV reactivation may develop with disease alterations or biological drug use (9, 10). HBV reactivation may occur in a patient who is an inactive HBsAg carrier or who has a resolved HBV infection. This is defined by the seroconversion of negative HBV DNA, or increase >1 log10 IU/mL in HBV titer, and/or hepatitis B e antigen (HBeAg)reversion, and the occurrence of active necroinflammatory liver disease characterized by a five-times higher ALT value. If the serum ALT level increases 2–3

Table 1. Patient groups according to viral hepatitis screening

		HBsAg	Anti-HBs	Anti-HBc total
Group 1	HBV seronegatives	-	-	-
Group 2	Immunized with vaccine	-	+	-
Group 3	With previous HBV infection	-	-	+
Group 4	With chronic HBV infection	+	-	+
Group 5	With healed HBV infection-Naturally immunized	-	+	+

HBsAg: hepatitis B surface antigen; Anti-HBs: antibody to hepatitis B surface antigen; Anti-HBc: antibody to hepatitis B core antigen; HBV: hepatitis B virus

Table 2. Patients to be screened for HCV infection

Patients showing a risky behavior

- IV and intranasal substance users

Patients exposed to risk

- Hemodialysis patients
- Patients with tattoos
- Exposure of security and health staff to blood with HCV
- Patients born to a mother with hepatitis C positive
- Patients who underwent blood–blood product transfusion before 1994 and those who underwent surgery

Other cases

- HIV positive cases
- Patients diagnosed with high aminotransferase levels or with liver disease

IV: intravenous; HCV: hepatitis C virus; HIV: human immunodeficiency virus

times more than baseline and the level of HCV RNA increases ≥1 log, HCV reactivation occurs. HBV and HCV reactivation may sometimes be in the form of fibrosing cholestatic hepatitis. Additionally, it was reported that reactivation develops after immunosuppressive use in patients previously exposed to HBV and who had developed immunity to it. "Covalently closed circular DNA" (cccDNA), functioning as a template during the replication of HBV, is found in the nuclei of hepatocytes of each patient with HBV infection. As the immune control on cccDNA is removed, HBV replication starts again in increased levels. On the other hand, the reactivation risk is high when occult HBV infection is present (11). Occult HBV infection is defined as the detection of HBV DNA in the serum at very low titers (<200 IU/mL) in lymphatic system cells and/or in liver tissue in HBsAg-negative patients.

This guideline comprises pre-treatment screening and follow-up recommendations, if necessary, with respect to viral hepatitides in rheumatology patients in whom it was planned to give biological drugs to in Turkey. Although this guideline is prepared for biological disease-modifying antirheumatic drugs (DMARDs), it is recommended to be also used for target-oriented DMARDS and medium–high dose corticosteroids (>7.5 mg prednisolone/day equivalent). It should be considered that the reactivation risk is higher when more than one immunosuppressive drug is used.

Patients are divided into four groups as very high, high, medium, and low-risk groups with respect to the HBV reaction risk according to HBV serology and the immunosuppressive regimen to be used.

1. Very high-risk patients (reactivation risk>20%)
   - Patients who are HBsAg (+) to hepatitis B core antigen (Anti-HBc) (+) and taking rituximab (RTX) and ofatumumab.
2. High-risk patients (reactivation risk 11-20%)
   - Patients who are HBsAg (–)/Anti-HBc (+) and taking rituximab and ofatumumab.
   - Patients who are HBsAg (+)/Anti-HBc (+) and have been taking anthracycline derivatives (doxorubicin or epirubicin) and >10 mg of prednisolone for ≥4 weeks.
3. Medium-risk patients (reactivation risk 1–10%)
   - Patients who are HBsAg (+)/Anti-HBc (+) or HBsAg (–)/Anti-HBc (+) and taking anti-TNF agents (etanercept, adalimumab, certolizumab, or infliximab), T cell co-stimulation inhibitor (abatacept), interleukin (IL)-12/IL-23 inhibitor (ustekinumab), integrin inhibitors (natalizumab orvedolizumab), and tyrosine kinase inhibitors (imatinib or nilotinib).
   - Patients who are HBsAg (+)/Anti-HBc (+) and have been using <10 mg of prednisolone for ≥4 weeks.
   - Patients who are HBsAg (–)/Anti-HBc (+) and have been using anthracycline derivatives (doxorubicin or epirubicin) and >10 mg of prednisolone for ≥4 weeks.
4. Low-risk patients (reactivation risk<1%)
   - Patients who are HBsAg (+) or HBsAg (–)/anti-HBc (+) and have been using azathioprine, 6-Mercaptopurine, methotrexate, intra-articular steroid, and corticosteroid at any dose for ≤1 weeks.
   - Patients who are HBsAg (–)/Anti-HBc (+) and have been using <10 mg of prednisolone for ≥4 weeks.

In the American Gastroenterology Association 2015 guidelines, although routine oral antiviral prophylaxis is recommended for high- and medium-risk patients, routine prophylaxis is not recommended for low-risk patients (12). HBV screening must be performed for all patients scheduled to receive biological treatment. Patients are divided into five groups according to the first screening tests about HBV (Table 1). HCV screening should not be conducted for all patients but only for those patients specified in Table 2.

Viral hepatitis screening recommendations before biological drug use in rheumatic diseases

The total number of recommendations is 10: the first eight are related to HBV screening and the last two are about HCV screening.

Recommendation 1

HBV screening must be conducted in all patients before biological treatment (TNF inhibitors, RTX, tociluzumab, abatacept, tofacitinib) (Figure1). If screening has not been conducted previously, the patient has to be screened during control visits.

Recommendation 2

The first dose of HBV vaccine should be administered before the treatment, if possible, and to

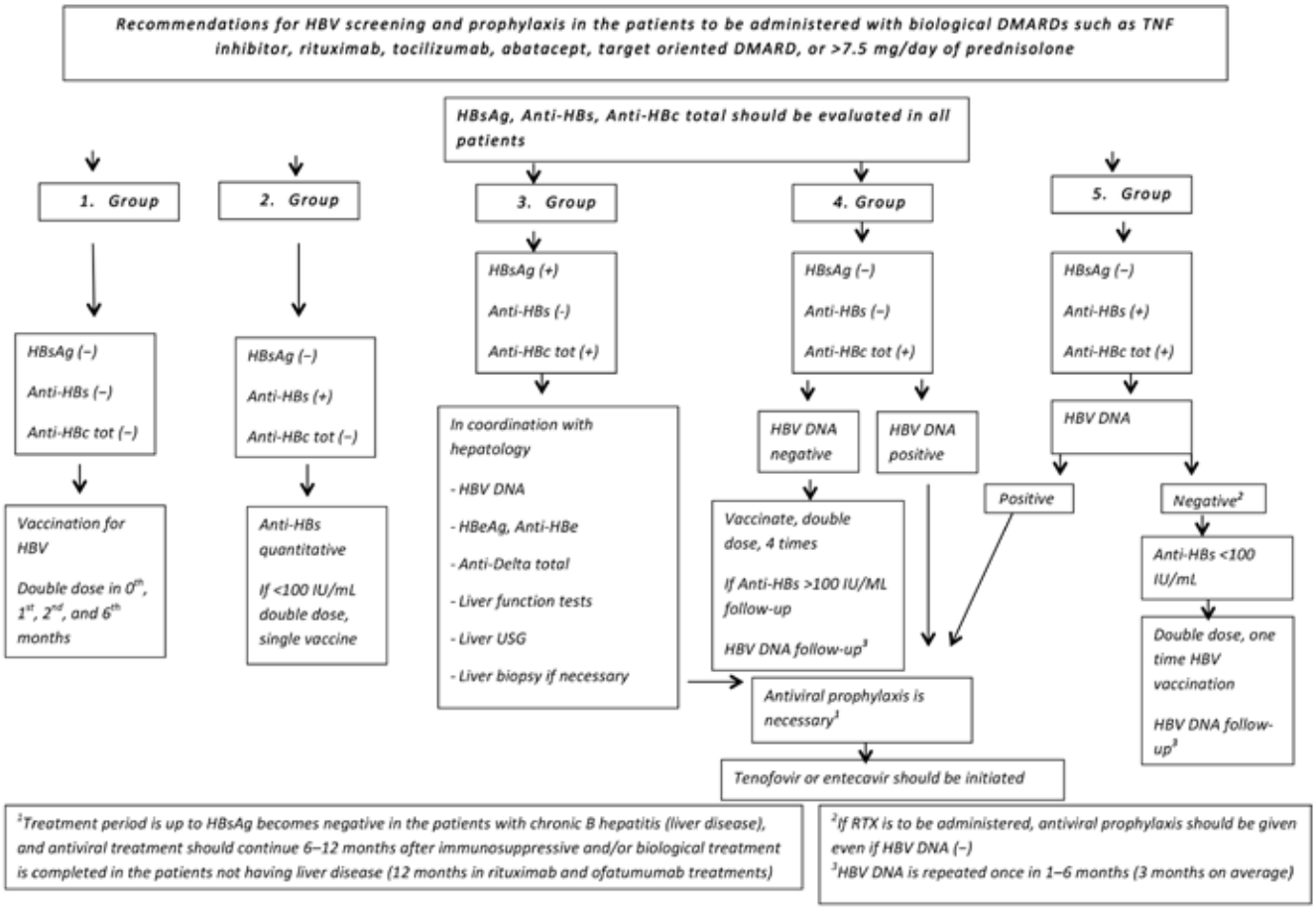

Figure 1. Algorithm for screening and prophylaxis of HBV in rheumatic diseases before biological drugs use

HBV: hepatitis B virus; DMARDs: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; HBsAg: hepatitis B surface antigen; Anti-HBs: antibody to hepatitis B surface antigen; Anti-HBc: antibody to hepatitis B core antigen; HBeAg: hepatitis B e antigen; Anti-HBe: antibody to hepatitis B e antigen

patients with all hepatitis B indicators as negative (Group 1). Because the vaccine response is low in patients receiving immunosuppressive treatment (12), it is recommended that vaccination should be administered as a double dose (two adult doses of HBV vaccine together) in the 0th, 1st, 2nd, and 6th months.

Recommendation 3

Patients in group 2 have been previously vaccinated [HBsAg–, antibody to hepatitis B surface antigen (Anti-HBs+, Anti-HBc tot–). If the Anti-HBs titer is ≥100 IU/mL, no additional operation is needed because it is protective. Biological treatment may be initiated. However, if Anti-HBs is <100 IU/mL, double-dose vaccination in one application is recommended, and biological treatment may be initiated.

Recommendation 4

When screening tests show HBsAg+, anti-HBs–, and anti-HBc total+ (Group 3), this may implicate the presence of ongoing chronic HBV infection. At this stage, HBeAg, anti-HBe, HBV DNA, anti-Delta tot, and liver function tests should be ordered for the evaluation of liver disease. Besides, liver ultrasonography is also recommended. Antiviral prophylaxis is necessary for these patients. It is ideal to make a hepatological evaluation at this stage.

- Irrespective of the HBV DNA titer, prophylaxis is initiated with oral antivirals (entecavir 0.5 mg and tenofovir 245 mg, 1 daily tablet), the genetic barrier of which is high and potent. Prophylaxis should be preferably initiated two weeks before the administration of immunosuppressive drugs or simultaneously at the latest (13).
- The treatment period should be until HBsAg becomes negative for patients with chronic B hepatitis. Oral antivirals having a protective purpose should be continued 6–12 months after immunosuppressive and/or biological treatments are completed. In cases in which drugs for B lymphocytes, such as rituximab and atumumab, are used, prophylaxis must be continued for 12 months after the completion of treatment.

Recommendation 5

When the screening test results show HBsAg–, anti-HBs–, but anti-HBc total+ (Group 4), this means that those patients have a history of previous HBV infection. In that case, HBV DNA should be evaluated to rule out occult HBV infection.

- If HBV DNA is positive, antiviral treatment should be initiated according to the 4th recommendation. If HBV DNA is negative, vaccination should be performed according to the above recommendations.
- HBV DNA should be evaluated in 1–6 month intervals (three months on average) in the group if HBV DNA is negative.
- If RTX and ofatumumab are to be given to the patient, antiviral prophylaxis should be applied even if the patient is HBV DNA negative.

Recommendation 6

When the screening test results show HBsAg–, anti-HBs+, and anti-HBc total+ (Group 5), this implicates the presence of resolved HBV infec-

tion and natural immunity against HBV. To be certain, an HBV DNA test is recommended for patients in this group.

- If HBV DNA is positive, antiviral prophylaxis should be given according to the above recommendations.
- If HBV DNA is negative and the anti-HBs titer is <100 IU/mL, double-dose booster vaccination is applied.
- Anti-HBs titer is not a decisive indicator for antiviral prophylaxis.
- The HBV DNA test should be repeated in 1–6 months intervals (three months on average) in the group if HBV DNA is negative. If HBV DNA becomes positive, antiviral prophylaxis is initiated.
- If RTX and ofatumumab are to be administered to the patient, antiviral prophylaxis should be applied even if the patient is HBV DNA negative.

Recommendation 7

Patients administered with oral antivirals are followed-up once in 3–6 months. If HBV DNA becomes positive despite antiviral prophylaxis with lamivudine, such patients should be evaluated with regard to lamivudine resistance and the antiviral treatment should be switched to tenofovir.

Recommendation 8

An anti-HCV test must be performed in individuals in the risk group for HCV infection (Table 2). However, anti-HCV screening must be conducted for all patients to take RTX.

Recommendation 9

HCV RNA must be evaluated in individuals found to be anti-HCV positive.

- If HCV RNA is negative, the test should be repeated three months later.
- HCV genotype must be determined in patients whose anti-HCV and HCV RNA are found to be positive, and they must be evaluated with respect to the presence of liver disease.
- The treatments, including TNF inhibitors, in HCV RNA patients generally do not deteriorate the disease, and so, these treatments may be used during follow-up. When the regimens, including RTX, are preferred, the patients must be closely followed-up with regard to HCV reactivation.
- ALT and AST tests must be repeated once a month and HCV RNA test must be repeated once every three months in HCV RNA positive patients initiated biological drugs. In case of HCV reactivation (≥3 times increase in ALT level and ≥1 log increase in HCV RNA titer), discontinuation of the immunosuppressive treatment must be considered (14, 15).

Recommendation 10

Currently, there is no prophylactic treatment to prevent HCV reactivation. However, since effective direct-acting anti-HCV drug combination regimes will be available in Turkey in the near future, HCV positive cases may be treated accordingly, unless there is a contraindication to those new agents.

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